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Pregnancy in a patient with adrenocortical carcinoma during treatment with Mitotane — a case report

Ciąża u pacjentki z rakiem kory nadnerczy w trakcie leczenia mitotanem — opis przypadku

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Abstract

We present the case of a female patient with virilising adrenocortical carcinoma treated surgically who conceived during adjuvant treatment with mitotane. We discuss the frequently erroneous routine treatment with oral hormonal contraception without thorough differential diagnosis in female patients with oligo-/amenorrhea and subsequent delay in the proper diagnosis of adrenocortical carcinoma.
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Key words: *adrenocortical carcinoma, mitotane, pregnancy*

Streszczenie

W pracy przedstawiono młodą pacjentkę z wirylizującym rakiem kory nadnerczy leczonym operacyjnie, która zaszła w ciążę w trakcie terapii uzupełniającej mitotanem. Omówiono jednocześnie często błędne, rutynowe leczenie tabletkami antykoncepcyjnymi pacjentek z niezdiagnozowanymi zaburzeniami miesiączkowania o typie oligo-/amenorrhea i wynikające z tego opóźnienie rozpoznania raka kory nadnerczy. **(Endokrynol Pol 2011; 62 (2): 186–188)**

Słowa kluczowe: *rak kory nadnerczy, mitotan, ciąża*

Introduction

Primary adrenocortical carcinomas (ACC) are very rare, with an incidence of approximately 1-2 per million population per year [1]. In Poland, in a group of 1,790 patients with incidentally-found adrenal tumours observed in one centre, primary adrenal cancers were found in 7.5% of cases [2]. ACC may be found incidentally or may manifest as an abdominal mass or a characteristic syndrome of hormonal oversecretion. Carcinomas with excessive hormonal production occur in up to 60% of patients, mostly women, and manifest as Cushing's syndrome and/or virilisation [3]. ACCs can develop at any age, but are usually diagnosed before the age of five or between the ages of 30 and 50 [1]. ACCs used to be considered as extremely aggressive tumours, with prognosis in the adult population worse than compared to that of children. Nowadays, survival may be higher than previously thought. The optimal treatment is complete surgical resection [4]; but because occult micrometastases are present at the time of initial presentation and surgery [5], additional treatment with Mitotane alone, or sometimes in combination with other cytotoxic agents, is recommended by many authors [1, 4, 7].

A case report

A female patient, aged 26, was admitted to the Department of Endocrinology for the first time in 2008 because of suspected adrenocortical carcinoma. At the age of 24, she had had secondary amenorrhea for a year with symptoms of hyperandrogenism, manifesting mostly as rapid development of hirsutism. After consultation with a gynaecologist, oral contraceptives were prescribed, which the patient took for another year until a severe abdominal pain occurred and an ultrasound examination was performed. A huge abdominal tumour was discovered. Computer tomography confirmed the presence of a tumour measuring 170 × 110 × 150 mm,

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which may have originated from the left adrenal. Hormonal assessment revealed markedly increased DHEAS concentration (> 1000 mg/dL), with low normal cortisol level (259.4, 137 nmol/L). Stimulatory tests to exclude adrenal gland insufficiency were not performed at that time. Left adrenalectomy was performed and adrenocortical cancer (stage II, [6]) was confirmed with the expression of Ki67+ in 1% of cells. Six weeks later, hormonal analysis showed normalisation of the androgens (DHEAS 88.55 mg/dL, androstendion 0.7 ng/mL, 17αOH progesterone 1.3 ng/mL, free testosterone 1.1 pg/mL). Imaging studies did not show local recurrence or metastases. Mitotane treatment was started and concentration of the androgens further decreased. The patient began to menstruate spontaneously, but irregularly, hence progestins were recommended for days 16–25 of each cycle. The patient was informed of the necessity of non-hormonal contraception.

Fourteen months later, the patient conceived and a twin pregnancy was confirmed. The patient and her partner were informed of the possible teratogenic effect of Mitotane, but they decided to continue the pregnancy. The serum concentration of the drug was 12.5 mg/mL, slightly below the therapeutic range (recommended therapeutic range: 14–20 mg/mL).

The course of the pregnancy was complicated by the risk of pre-term delivery in the 6th week of gestation, hence progesterone was prescribed. Unfortunately, in the 10th week of gestation, missed labour was diagnosed and abortion was induced. Evaluation of the patient performed one and six months later did not reveal progression of the ACC.

Discussion

The case presented here is extremely unusual. Although ACC can occur at any age, its manifestation in the third decade is rare.

Mitotane (Lysodren, o,p'-DDD, a congener of the pesticide dichloro-diphenyl-trichloroethane [DDT]), an adrenolytic and cytotoxic agent, has been used for 50 years in the treatment of adrenocortical carcinoma. The adrenolytic effect of the drug depends on its metabolic activation due to conversion to o,p'-DDA and o,p'-DDE. It affects mitochondria in adrenal cortical cells, where it inhibits pregnenolone and cortisol synthesis. The drug also alters the peripheral metabolism of steroids [7]. Toxic effect may vary depending on the tissue, i.e. the zona glomerulosa of the adrenals is more resistant and aldosterone deficiency may occur later than hypocortisolemia [8]. The gonadal toxicity of Mitotane is unknown. Some authors report anti-oestrogenic effects [9]. In our patient, the excessive concentration of androgens prior to surgery had suppressed ovarian function for at least two years. Adrenalectomy and the subsequent decrease in androgens resulted in the spontaneous normalisation of ovarian function. Even concomitant treatment with Mitotane did not further impair ovarian function. During the follow-up prior to pregnancy, normal ovarian function had been observed by ovulatory concentrations of LH, FSH and E2 (42.79 mU/mL, 6.75 mU/mL, 257.6 pg/mL, respectively) and ultrasonography.

Mitotane is a category C pregnancy risk factor, hence contraception is suggested for female patients of reproductive age [8]. However, we did not suggest oral contraception shortly after the adrenalectomy, because the patient did not have a sexual partner at that time, and we chose to wait for the androgen concentration to decrease and spontaneous menstruation to resume. Later, oral contraception was prescribed, but the patient did not take it because of negative past experiences and the cost. Although we did prescribe it, we still had doubts if hormonal contraception would be effective and safe. Mitotan has a hepatotoxic effect and, as mentioned above, it influences the peripheral metabolism of steroids and changes hepatic production of proteins. No studies have been performed on the interaction of both drugs and contraceptive effectiveness if taken together.

After pregnancy was confirmed, the initial thought was to cease treatment. But Mitotane has a long half-life, which is mainly due to its accumulation in adipose tissue and it is detected in blood even several months after the patient has ceased to take it. Thus during the critical period of organogenesis, our patient would still have high blood concentration of the drug, and neither our patient nor the foetus would have benefited if treatment had been stopped. On the other hand, pregnancy is a state of increased concentration of various growth factors that promote the development of the foetus [10]. Thus, fearing ACC progression, we decided to continue the treatment.

Unfortunately, a pathological examination was not performed following the abortion and we do not have data on possible foetal tissue damage.

In the past, the prognosis for patients with ACC was extremely poor. Nowadays, we have reports of the long-term survival of some patients and even successful pregnancies have been reported [11, 12]. We plan to treat the described patient with Mitotane for approximately five years and, if there are no recurrences, to cease treatment. After approximately a year, we plan to check the Mitotane serum concentration, and if it is no longer detectable we can then tell the patient that pregnancy is now possible.

Oral contraception has been used too often as the first line approach to restore monthly vaginal bleeding in patients with oligo-/amenorrhea instead of carrying out a thorough examination and making a diagnosis.

One should keep in mind that the evaluation of such patients requires the exclusion of hyperprolactinemia, abnormal thyroid function, PCOS, hyperinsulinemia, adrenal hyperplasia and androgen-secreting tumours [13]. In our opinion, which is also based on other tragic cases of women treated in our Department, differential diagnosis should focus above all on excluding adrenal or ovarian carcinomas, at least by performing an ultrasound examination, as these diseases have the highest mortality, and early diagnosis and proper treatment may save lives.

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